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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/553,869	10/21/2005	Rikke Hoegh Lorentsen	66611.000013	1881

20306 7590 04/07/2009

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EXAMINER	
SWOPE, SHERIDAN	

ART UNIT	PAPER NUMBER
1652	

MAIL DATE	DELIVERY MODE
04/07/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/553,869	LORENTSEN ET AL.	
	Examiner	Art Unit	
	SHERIDAN SWOPE	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 February 2009*.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4 and 6-51* is/are pending in the application.

4a) Of the above claim(s) *12 and 18-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,6-11,13-17 and 40-51* is/are rejected.

7)☒ Claim(s) *1,4,6-11,13-17 and 40-51* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *0209*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' filing of February 18, 2009, in response to the Action of October 2, 2008, is acknowledged. It is acknowledged that Claims 2, 3, and 5 have been canceled, Claims 1 and 4 have been amended, and Claims 40-51 have been added. Claims 1, 4, and 6-51 are pending. Claims 12 and 18-39 were previously withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Claims 1, 4, 6-11, 13-17, and 40-51 and are hereby reexamined.

Claims-Objections

Objection to Claims 1, 4, 6-11, and 13-17 for reciting non-elected subject matter is maintained. New Claims 40-51 are herein objected to for reciting non-elected subject matter.

Claim 1 is objected to because it is missing an "and" at the end of line 14; ie, --protease cleavage site "and"--.

Claim 4, penultimate line, is objected to for "adjacent the cleavage site", which should be "adjacent to the cleavage site".

Claim Rejections - 35 USC § 112-Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 11 and 46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the following reasons.

Claims 11 and 46 are rendered indefinite for failing to be encompassed by the claims from which they depend, Claims 1 and 40, respectively. In each case, the parent claim, Claims 1

and 40, recite the human Granzyme B, while the dependent claim Claims 11 and 46 respectively, recite the human, mouse, and rat Granzyme B. Therefore, Claims 11 and 46 are rendered indefinite for failing to be encompassed by the claims from which they depend.

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Rejection of Claims 7 and 8 under 35 U.S.C. 112, first paragraph/lack of enablement, because the specification does not reasonably provide enablement for producing any authentic protein having any activity of any somatotrophin, glucagon, insulin, interferon, or granzyme B by cleaving a fusion protein comprising any said authentic protein with human granzyme B, is maintained. Claims 42 and 43 are herein rejected under 35 U.S.C. 112, first paragraph/lack of enablement, for the same reasons. In support of their request that said rejection be withdrawn, Applicants provide the following arguments.

The Examiner has not provided any information or basis for the rejection. In addition, Example 3 shows the self-activating cleavage of IEAD-GrB-H6 and IEPD-GrB-H6. Both of these peptides include a Granzyme B cleavage site that is cleavable by human Granzyme B and both peptides include the sequence of GrB-H6.

These arguments are not found to be persuasive for the following reasons.

The specification fails to enable the skilled artisan to make and use the recited invention because the specification fails to disclose (i) all authentic proteins having any activity of any

somatotrophin, glucagon, insulin, interferon, or granzyme B and (ii) whether any fusion protein comprising any said authentic proteins can be used in the recited method. The making and testing of all encompassed fusion proteins clearly represents undue experimentation.

The instant claims recite production of Granzyme B by incubating a fusion protein, comprising said Granzyme B and a Granzyme B cleavage motif. with human Granzyme B, wherein the added human Granzyme B releases the Granzyme B from the fusion protein by cleavage of said Granzyme B cleavage motif. The skilled artisan would known that a fusion protein comprising Granzyme B and a Granzyme B cleavage motif would, more likely than not, release the Granzyme B by autolysis (as shown by Example 3 herein). Therefore, the specification has not enabled the skilled artisan to make and use a method for production of Granzyme B by incubating a fusion protein comprising said Granzyme B with human Granzyme B, wherein the added human Granzyme B releases the Granzyme B from the fusion protein by cleavage.

Written Description

Rejection of Claims 7 and 8 under 35 U.S.C. 112, first paragraph, because the specification does not reasonably describe production of any authentic protein having any activity of any somatotrophin, glucagon, insulin, interferon, or granzyme B by cleaving a fusion protein comprising any said authentic protein with human granzyme B, is maintained. Claims 42 and 43 are herein rejected 35 U.S.C. 112, first paragraph/written description, for the same reasons. In support of their request that said rejection be withdrawn, Applicants direct the Examiner to the specification, page 11, middle paragraph, as describing each of the polypeptides recited in the claims as a polypeptide of interest.

These arguments are not found to be persuasive for the following reasons. The current specification, filed June 13, 2008, does not have a middle paragraph on page 11. Thus, it is assumed Applicants are referring to the original specification, filed October 21, 2005. It is acknowledged that the middle paragraph on page 11 of the original specification asserts that the recited method can be used for the production of somatotrophin, glucagon, and insulin. However, said paragraph fails to describe production of granzyme B. Moreover, the specification fails describe the recited genus of methods for the production of any authentic protein having any activity of any somatotrophin, glucagon, insulin, interferon, or granzyme B by cleaving a fusion protein comprising any said authentic protein with human granzyme B such that the skilled artisan would recognize that Applicants were in possession of said genus.

As explained above, the skilled artisan would know that a fusion protein comprising Granzyme B and a Granzyme B cleavage site would, more likely than not, release the Granzyme B by autolysis (as shown by Example 3 herein). Therefore, the specification has not sufficiently described a method for production of Granzyme B by incubating a fusion protein comprising said Granzyme B and a Granzyme B cleavage site with human Granzyme B, wherein the added human Granzyme B releases the Granzyme B from the fusion protein by cleavage of said motif.

Claim 4 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the Inventors, at the time the application was filed, had possession of the claimed invention. Claim 4 introduces the limitation of "the penultimate amino acid at the N- terminus of the polypeptide of

interest is glycine". The specification fails to describe said limitation and, thus, Claim 4 is rejected under 35 U.S.C. 112, first paragraph, for introducing New Matter.

Additional Examiner's note: The specification states: "...it has now been established that Granzyme B protease may be generally used for cleaving off polypeptides of interest from fusion proteins, without the need for specific amino acid residues at the P1'-P4' positions" [0028].

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 9-11, 16, 17, 40, 44-46, 50, and 51 are herein rejected under 35 U.S.C. 103(a) as being unpatentable over Azad et al, 1994 in view of Harris et al, 1998 and further in view of Casciola-Rosen et al, 1999. Azad et al teach a GST-nef27 fusion protein (pg 651, pargs 2-3). Azad et al does not teach a GST-granzyme B cleavage motif-nef27 fusion protein or using said fusion protein to produce nef27. As taught by Azad et al nef27 contains Met-Gly at the N-terminus (pg 651, parg 2; encoded by ATG-GGT). It would have been obvious to a person of ordinary skill in the art to modify the fusion protein of Azad et al to incorporate the motif IEAD between the GST fusion partner and nef27 and then generate nef27 by cleaving the fusion protein with rat granzyme B, as taught by Harris et al (Fig 5D). Motivation to do so derives from the desire to produce nef27, which is critical for development of AIDS (Azad et al; Abstract). It would also be obvious to cleave said fusion protein with human Granzyme B, which as acknowledged by Applicants (pg 14, D of current remarks) was known in the art (also see

Casciola-Rosen et al). It would also be obvious to adapt the fusion protein rendered obvious by the above teachings to replace the GST fusion partner with a 6X-His fusion partner. Motivation to do so derives from the desire to use Ni/nitrilotriacetic acid resin for purification of the fusion protein, as taught by Harris et al (pg 27366, parg 3). The expectation of success is high, as the making and cleaving of fusion proteins is well-known in the art. Therefore, Claims 1, 9-11, 16, 17, 40, 44-46, 50, and 51 are herein rejected under 35 U.S.C. 103(a) as being unpatentable over Azad et al, 1994 in view of Harris et al, 1998 and further in view of Casciola-Rosen et al, 1999.

In support of their request that the prior analogous rejection be withdrawn, Applicants provide the following arguments, which are relevant here.

(A) While applicants agree with the Examiner's conclusion of a general motivation to produce nef27, that motivation alone is not sufficient to render the presently claimed method obvious. The motivation that the Examiner cites is simply the desire to make polypeptides in authentic form, be it nef27 or any other polypeptide. This general motivation does not lead one of ordinary skill in the art to choose the method of Harris, et al. for producing polypeptides.

(B) As discussed above, Harris, et al. does not teach producing a polypeptide of interest in authentic form.

These arguments are not found to be persuasive for the following reasons.

(A) Reply: MPEP 2143.01 [R-2] states the following. "There are three possible sources for a motivation to combine references: the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art." In the instant case, the nature of the problem to be solved is the desired to produce Nef27 protein for the study of AIDS, the teachings of the prior art are (i) the teaching of an authentic nef27 fusion

protein by Azad et al and the teachings of producing proteins from fusion proteins using the method of Harris et al, and the knowledge of persons of ordinary skill in the art is to combine the teachings of Azad et al and Harris et al to solve the problem.

(B) Reply: It is acknowledged that Harris, et al. does not teach producing a polypeptide of interest in authentic form. If Harris et al did so teach, this would be a rejection under 35 USC 102.

Claims 1, 4-6, 9-11, 16, 17, 40, 41, 44-46, 50, and 51 are herein rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Azad et al, 1994, Harris et al, 1998, and Casciola-Rosen et al, 1999 in view of Boutin et al, 1997. The teachings of Azad et al, Harris et al, and Casciola-Rosen et al are described above. Said combination does not teach preparing a protein of interest by providing a fusion protein comprising, from the N-terminal to C-terminal, a fusion partner, a granzyme B cleavage motif, and the protein of interest followed by contacting said fusion protein with granzyme B, wherein the protein of interest is an enzyme. Boutin et al teach that, like nef27, essentially all proteins that become myristoylated begin with Met-Gly at the N-terminus, including the enzyme calcineurin B (Table 3). It would have been obvious to a person of ordinary skill in the art to modify the fusion protein rendered obvious by the combination of Azad et al and Harris et al, such that the nef27 protein is substituted with calcineurin B. Motivation to do so derives from the desire to produce calcineurin B, a calcium-dependent phosphatase, using human Granzyme B (Casciola-Rosen et al). The expectation of success is high, as the making and cleaving of fusion proteins is well-known in the art. Therefore, Claims 1, 4-6, 9-11, 16, 17, 40, 41, 44-46, 50, and 51 are herein rejected under 35

U.S.C. 103(a) as being unpatentable over the combination of Azad et al, 1994, Harris et al, 1998, and Casciola-Rosen et al, 1999 in view of Boutin et al, 1997.

In support of their request that the prior analogous rejection be withdrawn, Applicants provide the following arguments, which are relevant here.

(C) The combination of Azad, et al. and Harris, et al. does not render obvious claim 1 for the reasons addressed above.

(D) The Examiner suggests that Boutin, et al. includes a protein beginning with Met-Gly at the N-terminus. Applicants do not agree that Table 3 of Boutin, et al discloses proteins, including calcineurin, with Met at the N-terminus. Indeed, the first line of the Abstract states that "N-myristolyation is an acylation process absolutely specific to the N-terminal amino acid glycine in proteins."

These arguments are not found to be persuasive for the following reasons.

(C) Reply: See (A) above.

(D) Reply: The skilled artisan would know that the N-terminal methionine is cleaved from the authentic protein co-translationally; see Boutin et al; pg 16, parg 6, which further cites Wilcox et al, 1987 and Deichaite et al, 1988. Deichaite et al specifically states: "Removal of the amino-terminal methionine residue from proteins is catalyzed when the nascent chain is approximately 20 amino acids long… myristylation occurs before the first 100 amino acids are polymerized..." (pg 4299, last parg). Thus, the authentic protein, encoded by the endogenous gene, has an N-terminal methionine.

Claims 1, 9-11, 13-17, 40, and 44-51 are herein rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Azad et al, 1994, Harris et al, 1998, and Casciola-Rosen et

al, 1999 in view of Sigma Inc, 1998 or Pharmacia, Inc. The teachings of Azad et al, Harris et al, and Casciola-Rosen et al are described above. Said combination does not teach a method wherein the granzyme B is immobilized. However, the use of immobilized proteases for generating a polypeptide from a fusion protein is well-known in the art; see, for example Sigma, Inc. In addition, it was well-known that proteins can be immobilized via the N-terminus, the C-terminus, or lysine residues (Pharmacia, Inc). It would have been obvious to a person of ordinary skill in the art to modify the method of rendered obvious by the combination of Azad et al and Harris et al to used immobilized granzyme B. Motivation to do so derives from the desire to circumvent the need to remove granzyme B from the generated polypeptide. The expectation of success is high, as the use of immobilized proteases for cleaving fusion proteins was well-known in the art. Therefore, Claims 1, 9-11, 13-17, 40, and 44-51 are herein rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Azad et al, 1994, Harris et al, 1998, and Casciola-Rosen et al, 1999 in view of Sigma Inc, 1998 or Pharmacia, Inc.

In support of their request that the prior analogous rejection be withdrawn, Applicants provide the following arguments, which are relevant here.

(E) Sigma Inc. and Pharmacia, Inc. do not cure the deficiency of the combination of Azad, et al., and Harris, et al. to render obvious claim 1.

These arguments are not found to be persuasive for the following reasons.

(E) Reply: See (A) above.

Allowable Subject Matter

No claims are allowable.

Applicant's amendment necessitated any new grounds of rejection presented in this Office action. Any new references were cited solely to support rejection(s) based on amendment or rebut Applicants' arguments. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Regarding filing an Appeal, Applicants are referred to the Official Gazette Notice published July 12, 2005 describing the Pre-Appeal Brief Review Program.

Final Comments

To insure that each document is properly filed in the electronic file wrapper, it is requested that each of amendments to the specification, amendments to the claims, Applicants' remarks, requests for extension of time, and any other distinct papers be submitted on separate pages.

It is also requested that Applicants identify support, within the original application, for any amendments to the claims and specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 571-272-0943. The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Nashed can be reached on 571-272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published application may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on the access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SHERIDAN SWOPE/
Primary Examiner, Art Unit 1652